REMARKS

Claims 42 to 82 are pending in this application. Claims 44, 47, 49 to 61 and 65 to 82 have been withdrawn. In view of their withdrawal from consideration, claims 67 to 82, directed to a non-elected invention, have been canceled without prejudice. Applicant reserves the right to prosecute the subject matter of the canceled claims in the present application and/or one or more related applications. New claims 83 to 89 have been added to the application. Support for the new claims can be found in the specification as originally filed, see, *e.g.*, the specification at page 91, lines 1-10 for claims 83 to 86 and page 28, lines 22-27 for claims 87 to 90. Thus, the new claims do not constitute new matter.

Accordingly, after entry of the present Amendment, claims 42 to 66 and 83 to 89 will be pending in the present application.

Information Disclosure Statement

Applicant notes that references B15, B16, C09, C10, C11, C12, C37, C38, C39 and C40 were crossed out on the revised PTO-1449 Forms filed July 20, 2007 and December 27, 2007. In particular, references B15 and B16 were crossed out on the revised PTO-1449 Form for failure to provide an English translation. References C09, C10, C11, C12, C37, C38, C39 and C40 were crossed out on revised PTO-1449 Form for failure to provide a date.

Applicant is submitting herewith a Supplemental Information Disclosure Statement with a revised PTO-1449 Form and copies of references B18-B22 and C78-C165. The copies of the references include an English translation of the abstract of the reference previously cited as B16 (resubmitted as reference B19) and a European patent and a Canadian patent that claim priority to the reference previously cited as B15 (resubmitted as reference B18 and B20). In addition, the revised PTO-1449 Form provides dates for the references previously cited as C09, C10, C11, C12, C37, C38, C39 and C40 (resubmitted as references C86, C87, C88, C89, C101, C102, C103 and C104). Applicant respectfully requests that the Examiner consider the references listed on the revised PTO 1449 Form submitted herewith.

1. The Claim Objections should be held in abeyance

Claims 48 and 63 are objected to because they depend upon withdrawn claims. Applicant notes that these claims are withdrawn because they are directed to a non-elected species. Accordingly, Applicant respectfully requests that this objection be held in abeyance

until such time as there is allowable subject matter.

2. <u>The Rejection under 35 U.S.C. § 112, First Paragraph, Should be Withdrawn</u>

Claims 42, 43, 45, 46, 48 and 62-64 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. In particular, the Examiner alleges that the specification and the claims do not demonstrate a common structure and/or function for the genus of endonucleases and the genus of corresponding substrates required by the claimed methods. (see March 17, 2009 Office Action at pp. 4-6). For the reasons provided below, the rejection should be withdrawn.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. *See, e.g., Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed. Cir. 2003); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991). The Court of Appeals for the Federal Circuit has repeatedly considered the written description requirement and consistently found that *exacting detail is not necessary* to meet the requirement. *See e.g., In re Alton,* 76 F.3d 1168 (Fed. Cir. 1996) (stating that "[i]f a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, *even if [not] every nuance of the claims is explicitly described in the specification*, the adequate written description requirement is met")(emphasis added).

The criteria for determining sufficiency of written description set forth in Guidelines for Examination of Patent Applications Under the 35 U.S.C. § 112, paragraph 1, "Written Description Requirement" ("the Guidelines") (published in the January 5, 2001 Federal Register at Volume 66, Number 4, p. 1099-1111), specifies that:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice (see (1)(a) above), reduction to drawings (see (1) (b) above), or by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (see (1)(c), above). *Id.* at p. 1106, column 3, *l.* 13-29.

Where the specification discloses any relevant identifying characteristics, i.e., physical, chemical and/or functional characteristics sufficient to allow a skilled artisan to

recognize the applicant was in possession of the claimed invention, a rejection for lack of written description under Section 112, first paragraph, is misplaced. *Id.*

Furthermore, in accordance with the Guidelines, what is conventional or well known to one of skill in the art need not be disclosed in detail (*Id.* at p. 1105, column 3, lines 39-41), and, where the level of knowledge and skill in the art is high, a written description question should not be raised. *Id.* at p. 1106, column 1, lines 34-36. *See also Capon v. Eshhar*, 418 F.3d 1349, 1357 (Fed. Cir. 2005).

The specification does, indeed, provide sufficient written description of claimed methods. First, contrary to the Examiner's allegation, the specification provides sufficient detail regarding substrates for fungal tRNA splicing endonucleases that one skilled in the art would reasonably have concluded that Applicant was in possession of the substrates. The specification teaches that a substrate for fungal tRNA splicing endonuclease is "any nucleotide sequence recognized and excised by a eukaryotic splicing endonuclease, in particular, a fungal splicing endonuclease" (see specification at, *e.g.*, p. 28, lines 22-24). In particular, the specification teaches that a substrate for a fungal tRNA splicing endonuclease includes a nucleotide sequence comprising a tRNA intron and that the tRNA intron may comprise a mature domain or a bulge-helix-bulge structure of a precursor tRNA (see specification at, *e.g.*, p. 28, lines 24 to p. 29, line 1). The specification also provides techniques for the production of fungal tRNA splicing endonuclease substrates (see specification at, *e.g.*, p. 29, lines 4-16).

Moreover, as of the effective filing date, it was known in the art that the substrate for tRNA splicing endonuclease is highly conserved in eukaryotes (Trotta and Abelson, 1999, tRNA Splicing: An RNA World Add-On or an Ancient Reaction? In RNA World II, Tom Cech, Ray Gesteland and John Atkins (eds.), Cold Spring Harbor Laboratory Press ("Trotta 1")). In particular, Trotta 1 states that all intron-containing pre-tRNA molecules in eukaryotes have a conserved "clover-leaf" structure with an intron of 14-60 bases in length located in the same position, one base to the 3' side of the anticodon (Trotta at p. 561, line 17 to p. 562, line 1). Thus, the teaching in the specification regarding substrates for fungal tRNA splicing endonucleases coupled with the knowledge in the art regarding such eukaryotic substrates for tRNA splicing endonuclease would have reasonably conveyed to one skilled in the art that Applicant was in possession of the substrates.

Second, the specification provides sufficient written description of fungal tRNA splicing endonucleases. The specification teaches that a fungal tRNA splicing endonuclease

is an "enzyme that is responsible for the recognition of the splice sites contained in precursor tRNA and the cleavage of the introns present in precursor tRNA" (see specification at p. 31, lines 10-12). The specification teaches that techniques such as those utilized by Trotta et al., 1997, Cell 89: 849-858 ("Trotta 2") may be utilized to purify a fungal tRNA splicing endonuclease (see specification at p. 50, lines 4-5). Trotta 2 describes one technique in which affinity chromatography on immobilized tRNA was utilized to purify a fungal tRNA splicing endonuclease (see Trotta at p. 856, second column, third full paragraph, citing Rauhut et al., 1990, J. Biol. Chem. 265: 18180). In addition, the specification teaches that the yeast tRNA splicing endonuclease is a heterotetramer and identifies the four subunits of the *S. cerevisiae* enzyme as SEN54 (GenBank No. YPL083), SEN34 (GenBank No. YAR008w), SEN2 (GenBank No. M32336) and SEN15 (GenBank No. YMR059w) (see specification at p. 31, lines 17-20). Further, as of the effective filing date, subunits of tRNA splicing endonuclease for other species were known, in particular, the SEN34 subunit of the endonuclease of *Schizosaccharomyces pombe* was known (Lucas *et al.*, 2000, Yeast, 16:299-306 ("Lucas"; reference C93 on the revised PTO-1449 Form submitted herewith); see p. 302, col. 2, line 13 to p. 303, col. 1, line 2).

Moreover, none of the claims under examination require that the endonuclease be isolated or purified. In particular, claim 46 (and claims dependent therefrom) is directed to a method comprising "contacting a compound or a member of a library of compounds with a *fungal cell* containing the fungal tRNA splicing endonuclease and the substrate" (emphasis added). The specification teaches that "a cell or cell line of any fungal species well-known to one of skill in the art may be utilized in accordance with the methods of the invention" (see specification, page 12, lines 12-13). The use of a "fungal cell" containing the tRNA splicing endonuclease does not require the actual identification and purification of the endonuclease. It merely requires evidence that the fungal cells contain the tRNA splicing endonuclease, which the specification teaches could be identified by the cleavage of introns present in precursor tRNA (see specification at p. 31, lines 10-12). Thus, even if the subunits of fungal tRNA splicing endonuclease were not known as of the effective filing date of the application, the specification would have conveyed to one of skill in the art that Applicant was in possession of the claimed methods.

In view of the foregoing, Applicant submits that claims 42, 43, 45, 46, 48 and 62-64 do not lack written description under 35 U.S.C. § 112, first paragraph. Accordingly, Applicant respectfully requests that the rejection be withdrawn.

3. The Rejection under 35 U.S.C. § 103(a) Should be Withdrawn

Claims 42, 43, 45, 46, 48 and 62-64 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Tocchini-Valentini et al., International Publication No. WO 01/92463 ("Tocchini-Valentini"), in view of Gontarek, International Publication No. WO 00/67580 ("Gontarek"). In particular, the Examiner alleges that Tocchini-Valentini teaches methods of monitoring tRNA splicing endonuclease activity on various target molecules and Gontarek teaches methods for screening for a compound to modulate splicing reactions. The Examiner concludes that it would have been obvious to a person of ordinary skill in the art to screen for inhibitors of fungal tRNA splicing endonuclease because Tocchini-Valentini teaches the use of yeast cells as a source of tRNA splicing endonuclease and Gontarek teaches the need to screen for compounds that are inhibitors of the RNA splicing machinery so that various useful compounds such as fungicidal compounds can be identified (see March 17, 2009 Office Action, p. 9). For the reasons below, the rejection should be withdrawn.

A finding of obviousness requires that "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. §103(a). In its recent decision addressing the issue of obviousness, *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 USPQ2d 1385 (2007), the Supreme Court stated that the following factors set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966) still control an obviousness inquiry: (1) the scope and content of the prior art; (2) the differences between the prior art and the claimed invention; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *KSR*, 127 S.Ct. at 1734, 82 USPQ2d at 1388 quoting *Graham*, 383 U.S. at 17-18, 14 USPQ at 467.

The *KSR* Court rejected a rigid application of the "teaching, suggestion, or motivation" test previously applied by the Court of Appeals for the Federal Circuit. *KSR*, 127 S. Ct. at 1739 USPQ2d at 1395. However, the Supreme Court affirmed that it is "important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does . . . because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." *KSR*, S.Ct. at 1741, 82 USPQ2d at 1396. Thus, consistent with the

principles enunciated in *KSR*, a *prima facie* case of obviousness can only be established by showing a suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference and to carry out the modification with a reasonable expectation of success, viewed in light of the prior art.

Thus, the principles set forth in *Graham*—which are still good law post-KSR—require that both the suggestion and the expectation of success must be found in the prior art, and not derived from knowledge gained from the applicant's disclosure.

After the *KSR* decision, the Board of Patent Appeals and Interferences has continued to shape the contours of the obviousness inquiry. The Supreme Court in *KSR* stated that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 127 S.Ct. at 1741, 82 USPQ2d at 1389. Following *KSR*, the Board stated that "[i]t is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art." *Ex Parte El-Naggar*, WL 2814131 at *3 (BPAI 2007) (citing *In re Hedges*, 783 F.2d 1038, 1041 (Fed. Cir. 1986) (quoting *In re Wesslau*, 353 F.2d 238, 241 (C.C.P.A. 1965))).

As acknowledged by the Examiner, Tocchini-Valentini does not teach or suggest a method that includes "assaying for a compound that can reduce (or inhibitor *[sic]*) RNA splicing as recited in claims 42, 43, 46 and 48", or "a fungal cells such as a yeast cell recited in claims 46, 63 and 64" (see March 17, 2009 Office Action at p. 8). Rather, Tocchini-Valentini describes utilizing the characteristics of the first step of the tRNA splicing reaction (*i.e.*, cleavage of the pre-tRNA substrate), particularly the specificity of cleavage, to develop a *method of cleaving a target RNA molecule* that has a bulge-helix-bulge conformation by exposing said RNA to a eukaryotic or archael tRNA splicing endonuclease. Tocchini-Valentini describes the use of the RNA cleavage method for the removal of unwanted RNA molecules from cells (see p. 9, paragraph [0031]), the detection of the presence of particular types of RNAs (see p. 9, paragraph [0030]), the cleavage of a target RNA into defined ends with a 2',3' cyclic phosphate capable of being ligated (see p. 8, 9, paragraph [0029]), as well as the degradation of particular targeted RNAs (see p. 9, paragraph [0029]). There is no teaching or suggestion in Tocchini-Valentini that tRNA splicing endonuclease may be used as a drug target and to screen for compounds that modulate the activity of fungal tRNA splicing endonuclease. Moreover, there is no teaching or suggestion in Tocchini-Valentini of

utilizing in any method a nucleic acid comprising a tRNA intron within the *mature domain* of a precursor tRNA (see claims 87 to 89), which is considered the natural substrate of eukaryal tRNA splicing endonuclease (see specification p. 8, lines 31-33). Thus, Tocchini-Valentini does not teach or suggest the claimed methods.

The deficiencies in Tocchini-Valentini are not cured by Gontarek. Gontarek relates to methods of screening for compounds that modulate fungal *pre-mRNA* splicing. Gontarek describes "a method of screening for a compound modulating a pathogen or non-pathogen *splicing reaction* comprising the steps of contacting a *splicing reaction mix* with a candidate compound and identifying a compound modulating the splicing reaction." (see p. 2, lines 7-10; emphasis added). According to Gontarek, the definition of a "splicing reaction" is "any or all steps in the maturation of a eukaryotic *pre-mRNA*, including but not limited to lariat formation, branchpoint formation, spliceosome formation (or any aggregation of splicing factors or proteins on an *mRNA*, *pre-mRNA* or polynucleotide splicing signal) ... or protein bound to any RNA sequence that is, or is derived from, a *pre-mRNA* any sequence [sic]." (see p. 9, lines 26-31; emphasis added). In addition, "splicing reaction mix (es)" is defined as "a composition that allows a *pre-mRNA* to undergo a splicing reaction." (see p. 9, lines 32-33; emphasis added). Gontarek also describes "a method of [sic] wherein the splicing reaction comprises at least one component of a pathogen or non-pathogen *spliceosome*." (see p.12, lines 16-17; emphasis added). It is well-known in the art that "spliceosome" refers to a complex of RNA and protein subunits that remove the non-coding introns from unprocessed *mRNA* (Stryer, 1999, Chapter 33: RNA Synthesis and Splicing *in* Biochemistry, ("Stryer"); see p. 862-864).

In contrast, claim 1 of the present application is directed to a method for identifying a compound that modulates fungal *tRNA splicing endonuclease* activity. Thus, the subject matter of claim 1 is distinguished from the subject matter of Gontarek by providing a specific target for the screening assay that is a component of the *tRNA*, not mRNA, splicing machinery, and which is tRNA splicing endonuclease.

There are fundamental differences between mRNA splicing and tRNA splicing that would not suggest to one of ordinary skill in the art to substitute one splicing pathway for another. Although both mRNA splicing and tRNA splicing involve the removal of introns, the mechanism of action for the removal of introns from pre-mRNA is very different from the removal of introns from pre-tRNA (Abelson *et al.*, 1998, J Biol Chem., 273:12685-688 ("Abelson"); see p. 12685, col. 1, first paragraph). It is well known in the art that the

substrates, mechanism of action and factors involved in the mRNA and tRNA splicing pathways are completely different.

First, the substrate of the mRNA splicing reaction is an intron in a pre-mRNA molecule, which has a *different role* than a pre-tRNA molecule. mRNA, or messenger RNA, is the *template for protein synthesis* and transfers genetic information from the nucleus to the ribosomes, which are the sites of protein synthesis in the cytoplasm (Stryer, 1999, Chapter 5: Flow of Genetic Information, *in* Biochemistry; see p. 96, lines 19-22). tRNA, or transfer RNA, is the *adaptor molecule in protein synthesis* and its role is to carry specific amino acids in an activated form to the ribosome for polypeptide formation during translation (Stryer, 1999, Chapter 34: Protein Synthesis *in* Biochemistry; see p. 875-876). Moreover, the *identifying features* of the introns and their *recognition by the splicing machinery* are different between mRNA molecules and tRNA molecules in eukaryotes. mRNA introns are between 50 and 10,000 nucleotides in length and have a common structural motif, defined by a sequence that begins with the nucleotides GU at the 5' splice site and ends with the nucleotides AG at the 3' splice site, as well as an internal site located between 20 and 50 nucleotides upstream of the 3' splice site called the branch site (see Stryer, p. 860-861). The sequences at the 5' splice site and the 3' splice site, as well as the branch site, are recognized by the splicing machinery (described below) and thus play an important role in the splicing of the intron (see Stryer, p. 862-864). In contrast, tRNA introns are small (14 to 60 nucleotides in length), are located in the same position (one base to the 3' side of the anticodon in the tRNA molecule) and have no sequence conservation around the splice sites (Trotta and Abelson, 1999, tRNA Splicing: An RNA World Add-On or an Ancient Reaction? In RNA World II, Tom Cech, Ray Gesteland and John Atkins (eds.), Cold Spring Harbor Laboratory Press ("Trotta"); see p. 561, second paragraph and p. 570, second paragraph). However, they have a conserved base pair (the A-I base pair) between a base of the 5' exon immediately following the anticodon stem and a base in the single-stranded loop of the intron that is required for cleavage of the 3' splice site (see Trotta p. 562, first paragraph). tRNA introns are recognized either by reference to the mature domain of the tRNA molecule, whereby the tRNA splicing endonuclease (further described below) recognizes the mature domain and measures the conserved distance to the splice sites (see Trotta, p. 570, second paragraph), or by reference to the bulge-helix-bulge structure (see Trotta p. 579, first paragraph).

Second, the mechanism of action of mRNA splicing is significantly different from the mechanism of action of tRNA splicing. Pre-mRNA is spliced by the spliceosome, which is a large RNA-protein complex comprising small nuclear ribonucleoproteins (snRNPs) (see

Stryer, p. 862-863). The spliceosome excises the intron and ligates the exons of pre-mRNA through two transesterification reactions, releasing the intron in the form of a lariat (see Stryer, p. 861-862). In contrast, pre-tRNA is spliced by three protein enzymes, in three distinct steps (see Abelson; p. 12685, col. 2, second paragraph). In the first step, the tRNA endonuclease cleaves the pre-tRNA substrate either in reference to the mature domain of the substrate or by recognizing the bulge-helix-bulge structure of the substrate. In the second step, the pre-tRNA is ligated by tRNA ligase, and in the third and last step of the splicing reaction, the 2'-phosphate generated by the ligase reaction is removed from the spliced tRNA by 2' phosphotransferase. Thus, given the differences between mRNA splicing and tRNA splicing, one of ordinary skill in the art would *not* substitute tRNA splicing for mRNA splicing.

Moreover, contrary to the Examiner's allegations, a person of ordinary skill in the art would not have been motivated to screen for compounds that modulate the activity of fungal tRNA splicing endonuclease because of any teaching by Gontarek regarding the need to screen for compounds that are inhibitors of the mRNA splicing machinery to identify compounds that are useful as fungicidal compounds (see March 17, 2009 Office Action, p. 9). Neither Tocchini-Valentini nor Gontarek provide any indication that a fungal *tRNA splicing endonuclease* might be a suitable drug target. In fact, given the conservation of the tRNA splicing endonuclease between humans and yeast, a person of ordinary skill in the art would *not* have been motivated to consider fungal tRNA splicing endonuclease as a potential drug target in humans. Zillman *et al.*, (Mol Cell Biol., 1991, 11:5410-5416 "Zillman")), for example, emphasizes the "apparent conservation of the endonuclease reaction between organisms as diverse as yeasts and vertebrates" (see p. 5411, paragraph bridging col. 1 and 2) and states that "endonuclease cleavage in yeast, wheat germ and vertebrate cells generates a 5' half molecule terminating with a 2',3' cyclic phosphodiester and a 3' half molecule beginning with a 5' hydroxyl, suggesting conservation of the endonuclease reaction among eukaryotes" (see Zillman, p. 5410, col. 1, second paragraph). Zillman further states that "the conservation of the entire yeast-like ligation pathway in vertebrate cells suggests that it is essential for the splicing of at least some tRNAs" (see p. 5415, col. 2, last paragraph), thus indicating that the tRNA splicing pathway might be important for cell viability. Tocchini-Valentini also acknowledges the importance of the tRNA splicing pathway to cell viability. Tocchini-Valentini states that "[a]ccuracy in tRNA splicing is essential for the formation of functional tRNAs, and hence for cell viability." (see p. 13, paragraph [0047]). Thus, one of ordinary skill in the art would have expected a compound that modulates the activity of a

fungal tRNA splicing endonuclease to also modulate the activity of animalia (in particular, a human) tRNA splicing endonuclease. Therefore, one of ordinary skill in the art would not have expected a fungal tRNA splicing endonuclease to be a reasonable drug target, in particular a target for an anti-fungal drug, because of the expected lack of selectivity for the fungal tRNA splicing endonuclease and the importance of the endoncuclease for cell viability.

In view of the foregoing, the rejection of claims 42, 43, 45, 46, 48 and 62-64 under 35 U.S.C. 103(a) should be withdrawn

CONCLUSION

Applicant believes that the present claims meet all of the requirements for patentability. Consideration and entry of the amendments and remarks made herein into the file history of the present application are respectfully requested. The Examiner is invited to contact the undersigned if any issues remain.

Respectfully submitted,

Date: August 17, 2009

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